

INFLUENCE OF PREVIOUS SALT REGIME ON EXCRETIONS OF CHLORINE, SODIUM, AND POTASSIUM DURING THE CHLORIDE CONCENTRATION TEST OF DE WESSELOW

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I. CHLORIDE EXCRETION

There have been many attempts to estimate renal function from a study of urinary chloride excretion or concentration. The salt test introduced by Schlayer (1) was later discredited because of the effect of extra-renal factors. It was shown particularly by Rowntree and Fitz (2) that a previous salt-free diet placed the organism in a state of apparent salt unsaturation, and that a subsequently administered dose of salt would be retained unusually long, even though the kidneys were normal. However, de Wesselow (3) has recently proposed a somewhat different test for renal chloride excretion. He gives 4 grams of KCl in 200 cc. of water without regard to the previous diet or regime of the patient, and determines the chloride concentration of the urine during each of the three subsequent hours. The maximum chloride concentration (normally approximating 0.90 per cent Cl) is taken as indicating the maximum concentrating power of the kidney.

De Wesselow's test differs from Schlayer's in that he uses KCl instead of NaCl, and bases his conclusions upon the maximum chloride concentration attained in the urine rather than upon the period of time required for complete elimination of the ingested dose.

It seemed desirable to ascertain whether the de Wesselow test would yield results reasonably independent of the previous regime of the patient. We have, therefore, tried it on three patients after alternating chloride-free and chloride-containing diets.

Method of Investigation

The patients were selected to give a considerable variation in age, general health, type of nephritis and state of renal function. None

had subcutaneous edema or fluid in the serous cavities at the time the investigation was begun. On each type of diet sufficient time was allowed for a balance to be struck between salt intake and output or for the weight to become constant. In case 1, however, salt feeding had to be interrupted sooner than planned, owing to the onset of nausea and vomiting. The de Wesselow test was carried out at the end of each particular diet-period, the salt intake was then changed, and the test was repeated after an equilibrium between salt ingested and salt excreted had been again attained. Not over 6 grams of salt a day was added to the diet during the period of salt administration. The salt-free diet averaged less than one gram of salt a day, estimated from the known salt content of the milk in the diet, the other foods being so chosen as to contain only insignificant quantities of salt, which are not included in the estimate of the daily salt intake.

The test itself was begun from 45 minutes to 90 minutes after breakfast. Four grams of KCl were given with 200 cc. of water by mouth and the urine was collected hourly for three consecutive hours, during which period no food nor fluid was allowed. The urinary chloride concentration was determined by the usual Volhard titration method. The urea concentration index, indicating the number of times the kidneys concentrate the blood urea in the urine, was determined as described in a previous paper from this laboratory (4).

Case reports

Case 1. G. O., age 48, carpenter, was admitted November 4, 1925, complaining of shortness of breath. Nocturia, polyuria and dyspnea on exertion came on during the preceding summer, but in the three weeks prior to admission the dyspnea had become very severe, preventing sleep. Associated symptoms were cough, oliguria, occipital headache and impairment of vision. There was no history of hematuria nor of edema. There had been scarlet fever in childhood. Examination showed a patient in severe dyspnea, with some cyanosis, signs of pulmonary congestion, marked generalized arteriosclerosis, B. P. 230/164, the left heart border 12 cm. from the midsternal line in the fifth interspace, gallop rhythm, a rough systolic aortic murmur, some enlargement of the liver, no ascites, slight edema of the legs and over the sacrum, arteriosclerosis of the retinal vessels and hemorrhages in the fundi. The urine showed albumin, few erythrocytes, many hyaline and granular casts. Digitalization produced marked clinical improvement within a week, and the edema disappeared. The hypertension and headaches continued and the eye-ground changes advanced to those of a typical

albuminuric retinitis. The functional findings indicate an advanced state of renal insufficiency. The patient's condition was fairly stable during the period of investigation.

Case 2. R. V., age 24, streetcar conductor, was admitted November 17, 1925, complaining of persistent edema of the legs. He never had a sore throat, but frequent colds in the head. After a rather severe cold in June, 1925, marked edema set in, along with nocturia, weakness, and shortness of breath upon exertion. Under proper treatment the edema cleared up somewhat and marked loss of weight was evident, due to loss of body tissue. Infected tonsils were removed in July, 1925. There was some improvement, but weakness, pallor, and edema of the legs hung on. Examination showed moderate pallor, no evidence of oral, nasal, or paranasal sinus infection, the left heart border 10.0 cm. from the mid-sternal line in the 5th interspace, a slight systolic murmur, B. P. 148/76 no fluid in the chest or abdomen, slight edema of the legs, the urine loaded with albumin, erythrocytes, leucocytes, fatty cells, and hyaline, granular and cellular casts; the eye-grounds negative. The edema cleared up rapidly but all the other findings remained obstinately stationary. Renal function in this case is only moderately impaired as compared with the state of case 1.

Case 3. R. G., age 11, school-boy, was admitted December 22, 1925, complaining of edema of the face and legs. This began four weeks previously, after an attack of acute abdominal pain, nausea and vomiting, without gross hematuria. There was no preceding acute infection but the patient had a chronic discharging mastoid sinus dating back to the original operation in January, 1924. There was no history of scarlet fever or sore throats. Examination showed a patient with mild bronchitis, puffiness and pallor of the face, a small draining sinus over the left mastoid region with local inflammatory edema of the scalp, considerable adenopathy of the left cervical chain, the left heart border 8.5 cm. from the midsternal line in the fifth interspace, a slight systolic blow at apex and base, B. P. 120/82, a small amount of fluid in the right chest, no ascites, moderate edema of the legs and over the sacrum, a leucocyte count of 17,600, normal hemoglobin, and in the urine much albumin, many erythrocytes, few leucocytes, and hyaline, granular and a few epithelial and red blood cell casts. The functional findings were nearly normal. Edema subsided rapidly and the general condition was good until January 19, 1926, when the mastoid sinus stopped draining. Fever, edema, and oliguria set in. On January 21, the walls of the sinus were incised to give better drainage. This was followed two days later by a sharp pyrexia, abdominal pain, nausea, vomiting, lumbar tenderness, increased hematuria, edema and leucocytosis. Diuresis and loss of edema followed in two days. A hemolytic streptococcus was grown from the pus in the mastoid sinus. In this case, as contrasted with the preceding two, renal function is now essentially normal, although temporary variations have occurred. In fact the urea concentration index has been persistently just at, or a little below, the lower limit of the normal range, in the

presence of an excellent phthalein output and a low blood urea nitrogen. During the last period of observation, noted in table 1, the urea concentration index indicates perfectly normal renal function for the first time.

Discussion of Results

Table 1 gives a summary of the chief functional findings in the three cases studied and illustrates the variations produced by the preceding type of diet—salt-containing or salt-free—in the de Wesselow chloride concentration test. The figures for the urea concentration index and the phthalein output represent the average of the determinations during the particular period. The maximum urinary chloride concentration was usually found in the third hour after administration of 4 grams of potassium chloride with 200 cc. water. Sometimes, however, this occurred in the second hour and was the figure used. Insufficient urinary volume was not a factor in this series of cases.

The most striking fact apparent from the table is the variation in the maximum urinary chloride concentration shown by each patient. In each of the three cases the de Wesselow test gave results indicating, apparently, much better chloride concentrating ability when the patient was on a salt-containing diet than when he was on a relatively salt-free diet. The difference between the values for the two periods amounted to several hundred per cent at times. That this difference in chloride concentration did not reflect a corresponding change in renal function is proved by the relatively small variation in the urea concentration index and phthalein figures. The consistency with which the chloride concentration went back to a low level when the patient was returned to a salt-free diet—other things remaining essentially equal—points to an extra-renal factor. This factor seems to be the chloride want of the body as a whole. When a patient has been on a salt-free diet for some time the tissues are depleted of their reserve chloride content, although the blood plasma may maintain a normal chloride concentration. Salt ingested under such conditions probably passes rapidly out of the circulation and into the tissues, becoming unavailable to the kidneys. When, on the contrary, as a result of several days of salt feeding, the tissues have saturated themselves with chloride, a test dose of salt is made rapidly available to the kidneys, and excretion, with concentration, follows.

TABLE 1

The effect of salt in the diet upon the urinary Cl concentration in the de Wesselow test

Case number	Name	Age	Period of observation	Daily NaCl intake	Urea concentration index* $\frac{U}{B} \sqrt{\frac{V}{W}}$	Phthalain in 2 hours	Maximum urinary Cl concentration in de Wesselow test†	
		years	1926	grams		per cent	per cent Cl	mM. Cl per liter
1	G. O.	48	January 23 to February 4	2.0	7	6		
			February 5				0.12	34
			February 8 to February 15	5.4	6	6		
			February 16				0.28	79
			February 17 to February 26	0.1	6	6		
			February 27				0.07	20
2	R. V.	24	1925-1926					
			December 5 to January 20	0.5	21	43		
			January 21				0.13	37
			January 23 to January 31	5.0	21	34		
			February 1				0.46	130
			February 4 to February 12	0.5	—	32		
			February 13				0.19	54
3	R. G.	11	1925-1926					
			December 23 to February 3	0.4	31	71		
			February 4				0.32	90
			February 5 to February 15	5.2	—	80		
			February 16				0.54	152
			February 18 to February 26	0.5	37	71		
			February 27				0.11	31
			February 28 to March 10	0.5	32	76		
			March 11				0.27	76
			March 12 to March 17	5.7	36	65		
			March 18				0.57	161
			March 21 to March 31	0.5	48	59		
			April 1				0.23	65

*The index is normally always above 35. U = urea concentration in urine, B = urea concentration in blood, V = cc. urine excreted per hour, W = body weight in kilos. The index has been discussed in a previous paper from this laboratory (4). It indicates the number of times the kidneys concentrate the blood urea in the urine, when the volume output is 1 cc. per kilo per hour.

†The maximum in normal subjects was found by de Wesselow to be 0.8 to 1.0 per cent of Cl, equivalent to 220 to 280 mM. per liter.

The use of sodium or potassium chloride perorally as a means of determining the concentrating ability of the kidney becomes practical, therefore, only when extra-renal factors are controlled. In view of the many complex inter-relationships between the chloride ion and other electrolytes in the maintenance of the water balance between body-fluids and cells, in the regulation of osmotic equilibrium, and in the acid-base mechanism, it would appear difficult to make any chloride test consistent. The situation is much more simple in the case of urea, because of its uniform distribution throughout the body as a whole and its relative unimportance in the equilibria mentioned above. Perhaps, if one could load the body sufficiently with chloride—by diets containing much salt—extra-renal factors would be minimized for a chloride test. Such a procedure, however, would be dangerous in many instances.

II. SODIUM AND POTASSIUM EXCRETION

The eliminations of sodium and potassium during the de Wesselow test were studied in order to determine which base accompanies the increased chlorine output. Studies of mineral metabolism in infants by Schloss (7) and by Meyer and Cohn (8) have shown that administration of KCl in relatively large doses (2 grams) causes a diuresis with an accelerated output of sodium as well as potassium. That a similar result follows in adults with varying types of nephritis could not, however, be concluded without direct evidence. Because the time available for this portion of the work was limited, experiments were completed on only two patients, and the periods of observation were limited to the three hours following the administration of KCl, as in the de Wesselow test. The aim has been limited to the answer of the question: Does the increased chloride output following the administration of KCl in the de Wesselow test indicate merely excretion of the administered potassium chloride, or is there also a washing out of sodium?

As in the experiments on chloride excretion, the patients were alternated on salt-free and salt-containing diet periods. Each regime was continued until the patient was in chloride equilibrium, or until the body weight had become stationary.

A control test was then carried out in which the patient received 200 cc. of water at the beginning of the test, and voided every hour thereafter for three consecutive hours. This was done as a control on the possible diuretic action of water itself. On the following day, a regular de Wesselow test was carried out, the patient receiving 4 grams of KCl and 200 cc. of water. Cases 2 and 3 were studied in this manner.

Methods of Analysis

The hourly specimens of urine were analyzed for chloride either by the usual Volhard titration or, where only small amounts of urine were available, by the plasma chloride method of Van Slyke (5).

Sodium and potassium were determined by the method of Goto (6) slightly modified as follows:

To 20 to 40 cc. of urine in a 50 cc. volumetric flask 10 cc. of 25 per cent trichloroacetic acid were added to precipitate the protein, which was regularly present in the urines of these patients. The flasks were filled up to the marks with water, and the solution was passed through an 11 cm. ash free dry filter paper. Of the filtrate 40 cc. were placed in a silica dish with 0.5 cc. of concentrated sulfuric acid, and evaporated as far as possible on a water bath. The dish was then transferred to an electric hot plate and heated, the temperature being raised slowly to avoid spattering. After evolution of fumes had nearly ceased, a few more drops of concentrated sulfuric acid were added to the charred mass, and the heating was repeated until fumes ceased coming off. The dish was then heated over a triple Bunsen burner for 30 minutes to burn off the carbon. The residue, which frequently contained a little carbon, was dissolved in 15 cc. of water and 5 cc. of concentrated hydrochloric acid. The solution was transferred to a 150 cc. flask, and the silica dish was washed into the flask with 4 portions of 5 cc. each of 0.5 N hydrochloric acid, which was warmed each time in the dish. To remove phosphoric and sulfuric acid from the solution in the flask 3 cc. of 10 per cent barium chloride were added, and a 10 per cent suspension of calcium hydroxide in sufficient amount to turn the mixture just alkaline to litmus. Usually 25 to 30 cc. of the lime suspension were required. The mixture was diluted up to volume and filtered through an ash-free 11 cm. folded paper. To remove barium and calcium from the filtrate, 100 cc. of the latter were treated in a 200 cc. flask with 25 cc. of a saturated ammonium oxalate solution and then ten per cent ammonium carbonate solution was added until no further precipitation occurred and the supernatant solution became clear. Usually 30 to 40 cc. of ammonium carbonate solution were required. The mixture in the flask was filled up to the 200 cc. mark with water, and filtered. Of the filtrate 50 cc. portions were placed in weighed silica dishes, and 5 cc. of concentrated hydrochloric acid were added to

each. The solutions were evaporated to dryness on the water bath, and were then heated on an electric hot plate until no more fumes of ammonium chloride were given off. Each dish was then heated cautiously over a small free flame just to a temperature sufficient to melt the mixture of alkali chlorides. (Overheating would cause loss by volatilization.) The combined weight of the KCl and NaCl was determined by weighing the cooled dishes.

The potassium was determined as perchlorate. To the combined chlorides in the silica dish 3 or 4 cc. of water were added, and 5 drops of perchloric acid of 1.12 specific gravity. The mixture was evaporated to dryness, and the residue was stirred up with 97 per cent alcohol containing 0.2 per cent of perchloric acid. The mixture was permitted to stand 20 minutes or more, and was then transferred to a weighed Gooch crucible. For completion of the transfer and washing 15 to 20 cc. of the same alcoholic solution were used. The precipitate of KClO_4 was dried for an hour or more at 110° and weighed. The KCl calculated from the KClO_4 found was subtracted from the combined weights of KCl and NaCl previously found, and the NaCl thus found by difference.

Blank analyses were done on the reagents, which proved to be free of potassium, but yielded 6.0 mgm. of NaCl. This was subtracted from the weight of the combined chlorides obtained in the urine analyses.

The precipitates weighed were often under 20 mgm., because of the necessity of using rather limited samples of urine collected during the hourly periods, and because of the small salt content of the urines, especially those collected during the periods in which the subjects were on approximate-chloride-free diets. Control analyses with similar amounts of pure KCl and NaCl gave quite good results, and we are confident of the approximate accuracy of the urine determinations. That the urines contained traces of sodium during the periods in which the analyses give negative results for this alkali, however, is probable, for the amounts analysed were not sufficient to show traces of the substance.

In a control analysis a standard solution was made up containing 1.0035 grams of NaCl and 1.0059 grams of KCl in 250 cc. of water, 20 cc. of this solution was carried through the above procedure. Duplicate 50 cc. portions of the final filtrate yielded 20.5 and 21.4 mgm. of NaCl + KCl, after subtracting the blank of 6.0 mgm. The theoretical value was 21.4 mgm. The weights of KClO_4 were 19.1 and 19.7 mgm., equivalent to 10.3 and 10.6 mgm. of KCl. The theoretical value was 10.7 mgm. By subtraction, NaCl was present to the extent of 10.2 and 10.8 mgm., respectively, theoretical yield being 10.7 mgm.

DISCUSSION OF THE BASE EXCRETION

The two cases were quite different in their tendency to form edema, and they showed accordingly different reactions to the ingestion of potassium chloride in the de Wesselow test (see table 2).

R. V. was a young man in whom an acute nephritis beginning about a year before had developed into a subacute chronic nephritis, with urea concentrating and phthalein excreting power reduced to about half normal, and with only a moderate tendency to form edema. When 5 grams of salt were added to his diet he would retain water up to a certain amount and show some weight increase, but in a few days, would reach a state of salt equilibrium, with output equal to intake and weight stationary, and without massive edema formation. When he was returned to a salt-free diet he readily eliminated the fluid previously retained.

R. G. on the other hand was a boy who would readily have been classed as a pure nephrosis case were it not for the constancy of hematuria, and a history of acute nephritis. His renal function was normal for urea and phthalein, but he had a tendency to edema formation difficult to control. During months of stay in the hospital on a salt-free diet he was never free from visible edema, which increased markedly when 5 grams of salt were added to the diet, and returned to its former state but slowly when the salt was discontinued.

When both patients had been on a salt-free diet for a sufficient period to reduce the saline stores of their bodies to the minimum thereby attainable, both reacted to the KCl administration with increased potassium output, accompanied by decrease rather than increase in the hourly Na output.

When, however, both had been on a diet with 5 to 6 grams of NaCl in it, they did not behave alike under the de Wesselow test. In the man R. V. there was an actual decrease in potassium output in the first and second hours, but an increased sodium output (unfortunately the urine of the third hour was lost). In the relatively much more edematous boy, R. G., there was increase in the potassium output, which did not become definite until the second hour; and it was accompanied by a decrease in sodium output.

R. G. Cont.	May 31	5.9	200 cc. H ₂ O	0.267	146.9	4.13	94.2	2.41	53.1	2.31	4.72	55
				0.402	112.5	3.17	66.8	1.71	37.3	1.62	3.33	28
				0.400	140.0	3.94	85.8	2.20	38.3	1.67	3.87	35
	June 1	5.9	4 grams KCl + 200 cc. H ₂ O	0.408	114.2	3.22	86.8	2.22	51.2	2.23	4.45	28
				0.427	128.1	3.61	103.6	2.65	37.5	1.63	4.28	30
				0.390	175.5	4.94	192.5	4.93	15.2	0.66	5.59	45

We do not wish from these two experiments to generalize on the relationship of "tendency to edema" and the efficiency of potassium salts in stimulating excretion of the sodium-containing edema fluids. But clinical experience with patients other than those tabulated here has shown that in some cases with great tendency to dropsy the addition of 10 grams of KCl daily to a previously chloride-free diet results in fluid retention instead of loss.

In both cases presented in table 2, the KCl administration during the periods with 5 to 6 grams of salt in the daily diet had but little effect on the Cl concentration in the urine. The chloride concentrating ability of these patients could have been determined as well without the administration of the potassium chloride as with it.

SUMMARY

The urinary chloride concentration test of de Wesselow was studied under controlled conditions upon three patients differing in age, general health, type of nephritis, and state of renal function.

The maximum chloride concentration obtained when the patients were consuming 5 to 6 grams of salt per day varied from 0.28 per cent Cl in case 1 to 0.57 per cent in case 3. With a salt-free diet the values ranged from 0.07 per cent Cl in case 1 to 0.32 per cent in case 3. Urea concentration index and phthalein were unaffected by the changes in salt intake. The results of the de Wesselow test, even when not complicated by the extrarenal factors present in edema, evidently depend greatly upon the salt content of the diet during the days preceding the test.

Comparison of results obtained with the different patients after diets of similar salt content shows a rough tendency for the chloride concentrating power, indicated by the de Wesselow test, to follow the urea concentrating power and phthalein output, but no approach to exact parallelism.

The hourly excretion of potassium and sodium during the de Wesselow test were followed in two nephritic patients. One (R. G.) had a maximal dropsical tendency, the other (R. V.) a moderate one. During the salt-free dietary periods, administration of KCl in the de Wesselow test decreased the sodium output in both patients. During

the salt-containing dietary periods the de Wesselow test caused the more edematous patient to retain sodium and the less edematous one to lose it.

In both patients the Cl concentration of the urine depended much more on the daily intake of NaCl than on the KCl given in connection with the test.

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